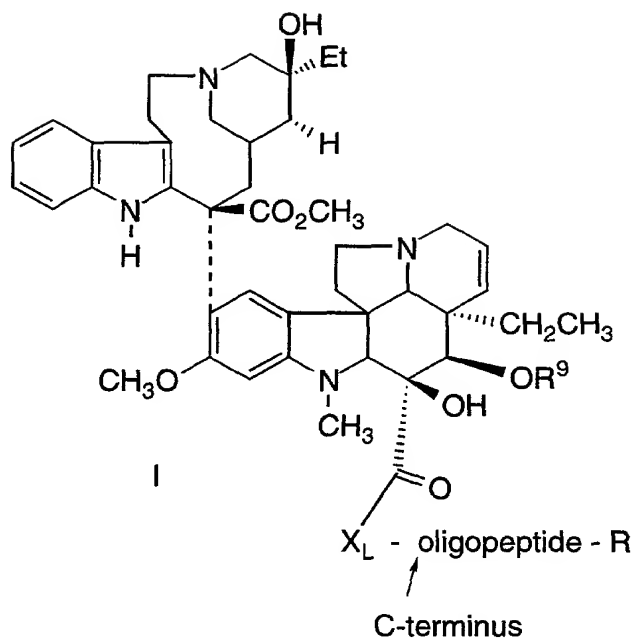


WHAT IS CLAIMED IS:

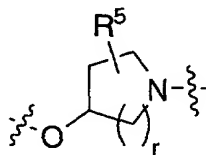
1. A conjugate which is useful for the treatment
of prostate cancer which comprises a cytotoxic agent attached to an
5 oligopeptide, wherein the oligopeptide comprises a sequence of amino
acids that is selectively proteolytically cleaved by free prostate specific
antigen and wherein the means of attachment is through a hydroxyalkyl-
amino chemical linker which is optionally substituted,
- 10 or the pharmaceutically acceptable salt thereof.
2. The conjugate according to Claim 1 wherein the
oligopeptide is attached to the chemical linker by an ester bond with
that bond comprising the hydroxyl moiety of the chemical linker.
- 15 3. The conjugate according to Claim 1 wherein the
cytotoxic agent is a vinca alkaloid cytotoxic agent.
4. The conjugate according to Claim 3 wherein the
20 cytotoxic agent is selected from vinblastine and 4-desacetylvinblastine.
5. A conjugate of the formula I:

T03090"42842660



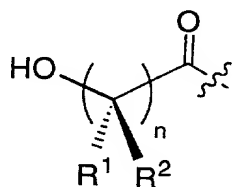
wherein:

- 5 oligopeptide is an oligopeptide which is specifically recognized by the free prostate specific antigen (PSA) and is capable of being proteolytically cleaved by the enzymatic activity of the free prostate specific antigen,
- 10 X_L is selected from -NH - (CR³₂)_u (CR⁴₂)_v - O - and

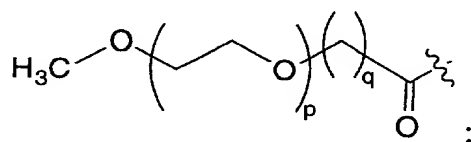


R is selected from

- 15 a) hydrogen,
b) -(C=O)R^{1a},
c)

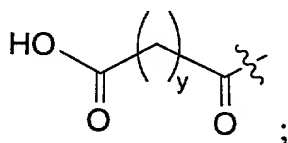


d)



5

e)



- f) ethoxysquarate; and
g) cotininyll;

10

R^1 and R^2 are independently selected from:

- a) hydrogen,
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, halogen, C₁-C₆ perfluoroalkyl, R^6O- , $R^6C(O)NR^6-$, $(R^6)_2NC(O)-$, $R^6_2N-C(NR^6)-$, $R^7S(O)_2NH$, CN, NO₂, $R^6C(O)-$, N₃, $-N(R^6)_2$, or $R^7OC(O)NR^6-$,
c) unsubstituted C₁-C₆ alkyl,
d) substituted C₁-C₆ alkyl wherein the substituent on the substituted C₁-C₆ alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R^6O- , $R^7S(O)_2NH$, $R^6C(O)NR^6-$, $(R^6)_2NC(O)-$, $R^6_2N-C(NR^6)-$, CN, $R^6C(O)-$, N₃, $-N(R^6)_2$, and $R^7OC(O)-NR^6-$; or

25

R¹ and R² are combined to form $-(CH_2)_s-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m, -NC(O)-, NH and -N(COR⁷)- ;

5 R^{1a} is C₁-C₆-alkyl, hydroxylated C₃-C₈-cycloalkyl, polyhydroxylated C₃-C₈-cycloalkyl, hydroxylated aryl, polyhydroxylated aryl or aryl,

10 R³ and R⁴ are independently selected from: hydrogen, C₁-C₆-alkyl, hydroxylated C₃-C₈-cycloalkyl, polyhydroxylated C₃-C₈-cycloalkyl, hydroxylated aryl, polyhydroxylated aryl and aryl, or

one R³ and one R⁴ are combined to form a $-(CH_2)_w-$, which is unsubstituted or substituted with one or two substituents selected from OH and C₁-C₆ alkyl; or

15 an R³ is combined with another R³ on the same carbon to form a $-(CH_2)_x-$; or

an R⁴ is combined with another R⁴ on the same carbon to form a $-(CH_2)_x-$;

20 R⁵ is selected from OH and C₁-C₆ alkyl;

R⁶ is selected from: hydrogen, aryl, substituted aryl, heterocycle, substituted heterocycle, C₁-C₆ alkyl and C₃-C₁₀ cycloalkyl;

25 R⁷ is selected from: aryl, substituted aryl, heterocycle, substituted heterocycle, C₁-C₆ alkyl and C₃-C₁₀ cycloalkyl;

30 R⁹ is hydrogen, (C₁-C₃ alkyl)-CO, or chlorosubstituted (C₁-C₃ alkyl)-CO;

n is 1, 2, 3 or 4;

p is zero or an integer between 1 and 100;

q is 0 or 1, provided that if p is zero, q is 1;

r is 1, 2 or 3;
s is 4, 5 or 6;
t is 3 or 4;
u and v are independently selected from: 0, 1, 2 or 3;
5 w is 2, 3 or 4;
x is 3, 4 or 5;
y is 1, 2 or 3;

or a pharmaceutically acceptable salt thereof.

10

6. The conjugate according to Claim 5 wherein:
oligopeptide is an oligomer that comprises an amino acid sequence
selected from:

- 15 a) AsnLysIleSerTyrGlnSer (SEQ.ID.NO.: 1),
b) LysIleSerTyrGlnSer (SEQ.ID.NO.: 2),
c) AsnLysIleSerTyrTyrIleSer (SEQ.ID.NO.: 3),
20 d) AsnLysAlaSerTyrGlnSer (SEQ.ID.NO.: 4),
e) SerTyrGlnSerSer (SEQ.ID.NO.: 5);
25 f) LysTyrGlnSerSer (SEQ.ID.NO.: 6);
g) hArgTyrGlnSerSer (SEQ.ID.NO.: 7);
h) hArgChaGlnSerSer (SEQ.ID.NO.: 8);
30 i) TyrGlnSerSer (SEQ.ID.NO.: 9);
j) TyrGlnSerLeu (SEQ.ID.NO.: 10);

- k) TyrGlnSerNle (SEQ.ID.NO.: 11);
 l) ChgGlnSerLeu (SEQ.ID.NO.: 12);
 5 m) ChgGlnSerNle (SEQ.ID.NO.: 13);
 n) SerTyrGlnSer (SEQ.ID.NO.: 14);
 o) SerChgGlnSer (SEQ.ID.NO.: 15);
 10 p) SerTyrGlnSerVal (SEQ.ID.NO.: 16);
 q) SerChgGlnSerVal (SEQ.ID.NO.: 17);
 15 r) SerTyrGlnSerLeu (SEQ.ID.NO.: 18);
 s) SerChgGlnSerLeu (SEQ.ID.NO.: 19);
 t) HaaXaaSerTyrGlnSer (SEQ.ID.NO.: 20);
 20 u) HaaXaaLysTyrGlnSer (SEQ.ID.NO.: 21);
 v) HaaXaahArgTyrGlnSer (SEQ.ID.NO.: 22);
 25 w) HaaXaahArgChaGlnSer (SEQ.ID.NO.: 23);
 x) HaaTyrGlnSer (SEQ.ID.NO.: 24);
 y) HaaXaaSerChgGlnSer (SEQ.ID.NO.: 25);
 30 z) HaaChgGlnSer (SEQ.ID.NO.: 26);
 aa) SerChgGlnSerSer (SEQ.ID.NO.: 106);

bb) SerChgGlnSerPro (SEQ.ID.NO.: 107); and

cc) SerChgGlnSerAbu (SEQ.ID.NO.: 108);

5 wherein Haa is a cyclic amino acid substituted with a hydrophilic moiety, hArg is homoarginine, Xaa is any amino acid, Cha is cyclohexylalanine, Abu is 2-aminobutyric acid and Chg is cyclohexylglycine;

10 or an optical isomer thereof.

7. The conjugate according to Claim 6 wherein:

Xaa is alanine, serine or isoleucine; and

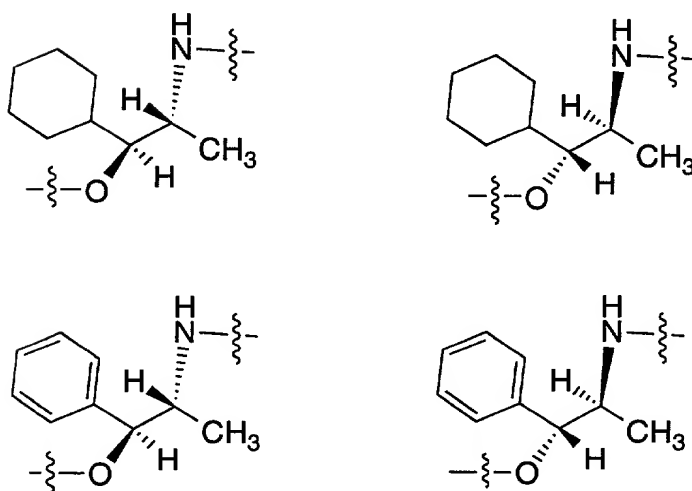
15 Haa is *trans*-4-hydroxy-L-proline;

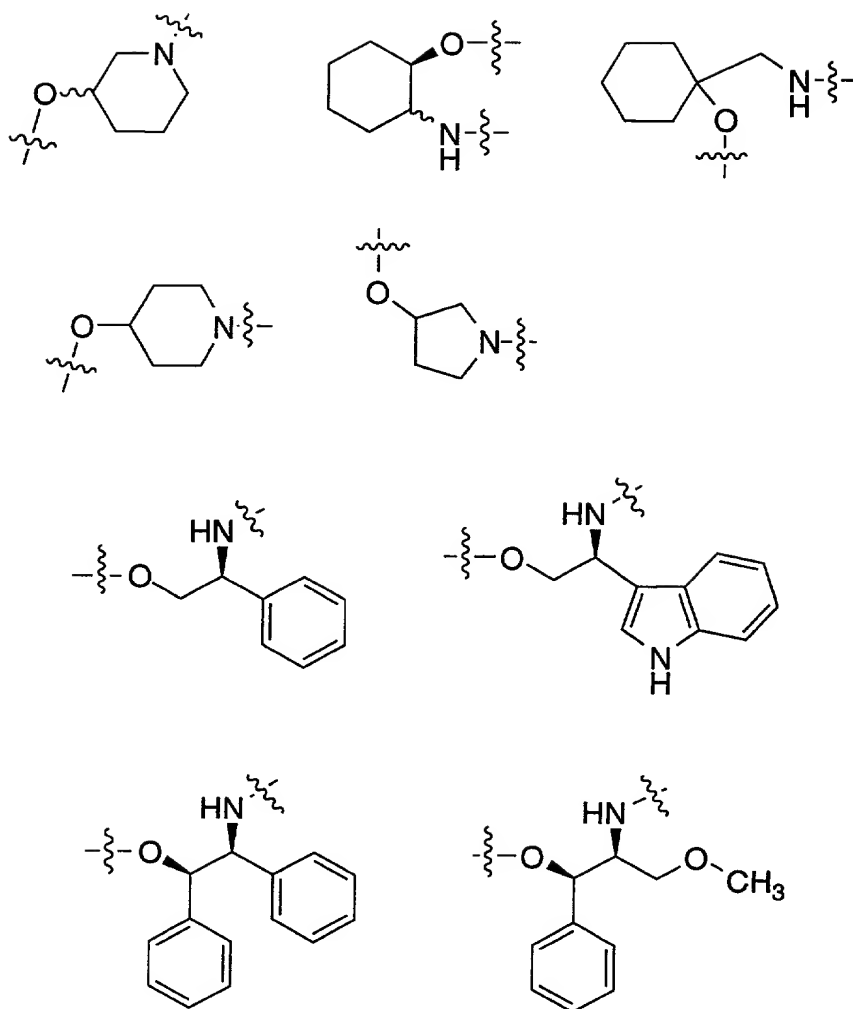
or an optical isomer thereof.

8. The conjugate according to Claim 5 wherein:

20

X_L is selected from the following group:





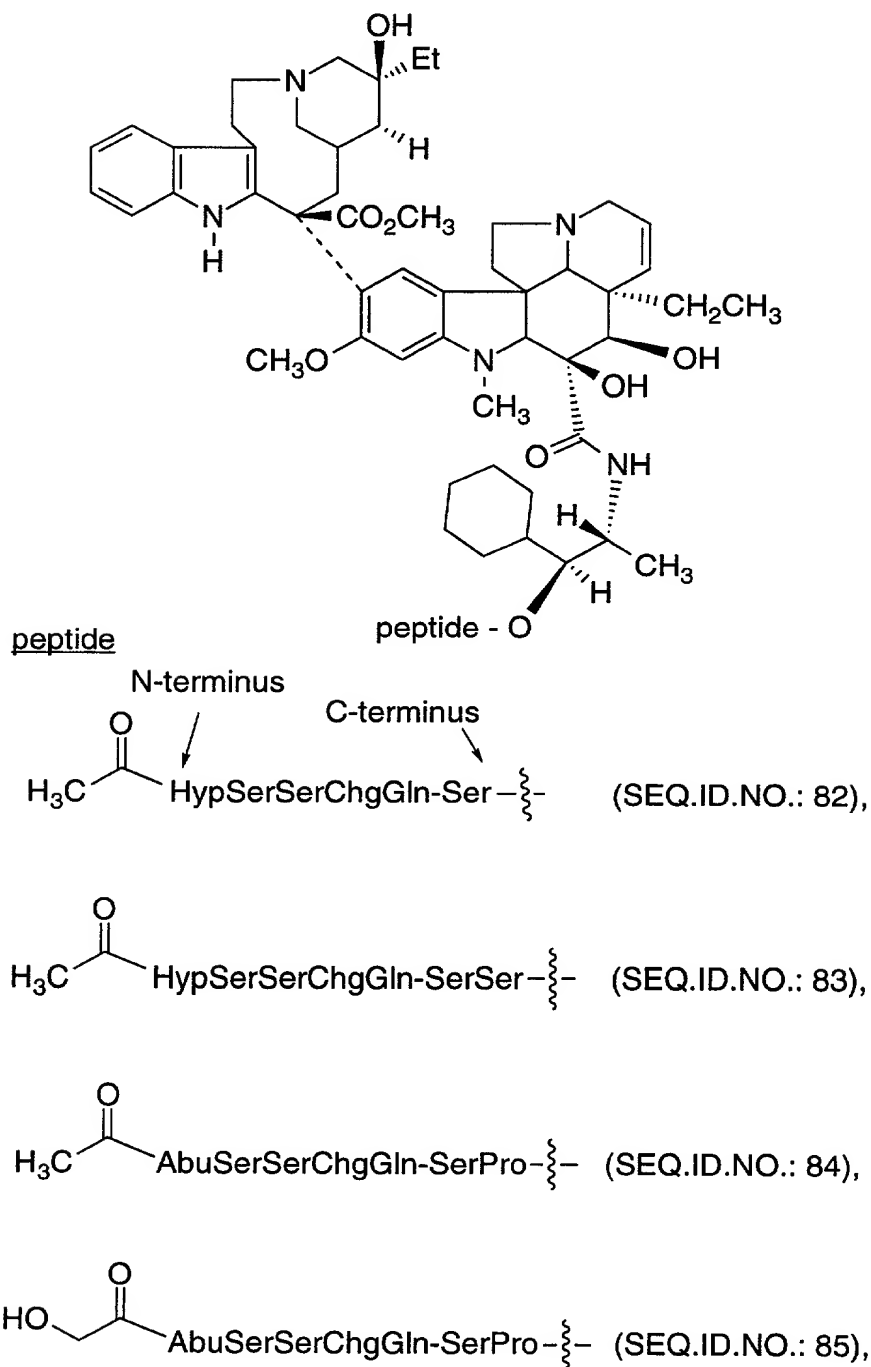
or an optical isomer thereof.

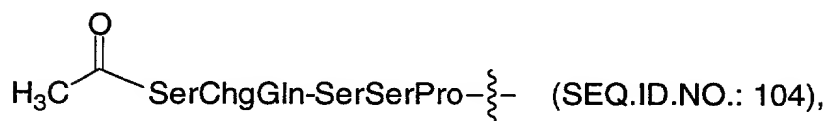
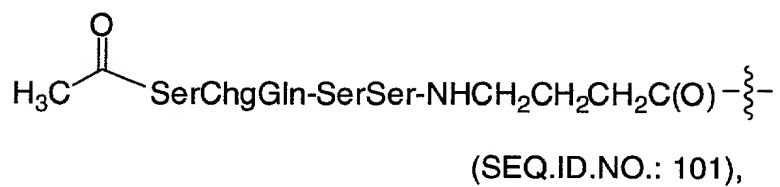
9. The conjugate according to Claim 5 which is selected from:

PEPTIDE-VIN CONJUGATE	SEQ. ID.NO.
Ac-(4-trans-L-Hyp)SSChgQ-SPheol-(dAc)-VIN	90
Ac-4-trans-L-HypSSChgQS-cyclopropylalaninol-(dAc)-VIN	91
Ac-4-trans-L-HypSSChgQS-cyclohexylalaninol-(dAc)-VIN	92
Ac-4-trans-L-HypSSChgQS-valinol-(dAc)-VIN	93
Ac-4-trans-L-HypSSChgQS-(HCAP)-(dAc)-VIN TFA salt	82
Ac-4-trans-L-HypSSChgQS-O-3(R)pyrrolidine-(HCAP)-(dAc)-VIN	82
Ac-4-trans-L-HypSSChgQ-SS-(HCAP)-(dAc)-VIN	83
N-hydroxyacetyl-AbuSSChgQ-SP-(HCAP)-(dAc)-VIN	85
Ac-SSChgQ-SP-(HCAP)-(dAc)-VIN	86
Ac-AbuSSChgQ-SP-(HCAP)-(dAc)-VIN	84
Ac-SChgQ-SP-(HCAP)-(dAc)-VIN	94
Ac-AbuSChgQ-SP-(HCAP)-(dAc)-VIN	95
Ac-SChgQSS-Sar-(HCAP)-dAc-VIN	96
Ac-SChgQS-Abu-(HCAP)-VIN	97
Ac-SChgQ-SS(4-trans-L-Hyp)-(HCAP)-dAc-VIN	98
Ac-SChgQSS(PIP)-(HCAP)-dAc-VIN	99
Ac-SChgQSS(HCAP)-dAc-VIN	100
Ac-SChgQSS-gammaAbu-(HCAP)-dAc-VIN	101
Ac-4-trans-L-HypSSChgQSP(HCAP)-VIN	102
Ac-SSChgQ-SSP-(HCAP)-dAc-VIN	103
Ac-SChgQ-SSP-(HCAP)-VIN	104
Ac-AbuSSChgQ-S-(HCAP)-VIN	105

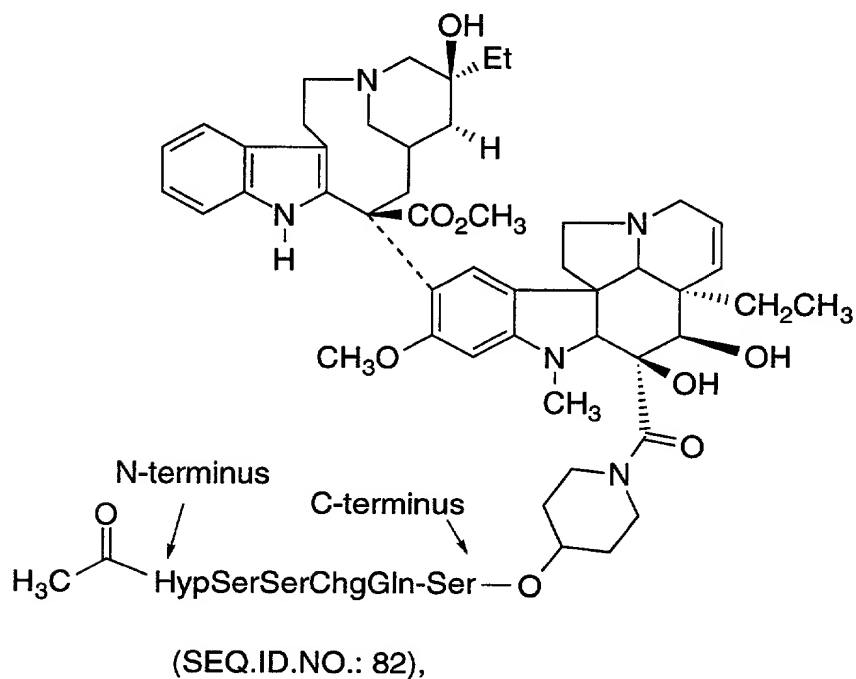
5 or a pharmaceutically acceptable salt or optical isomer thereof.

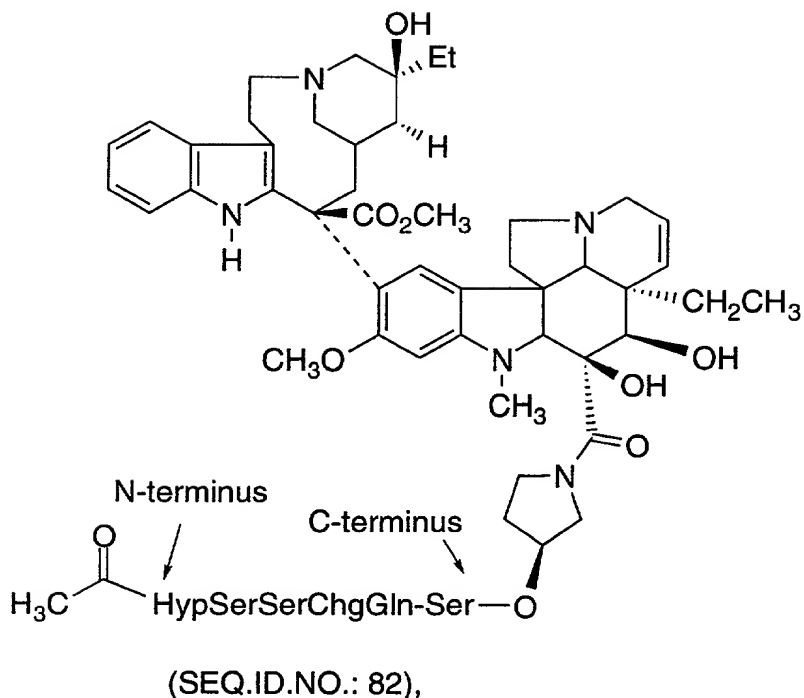
10. A compound which is selected from:



peptide

5





or the pharmaceutically acceptable salt or optical isomer thereof.

11. A pharmaceutical composition comprising a
 5 pharmaceutical carrier, and dispersed therein, a therapeutically effective
 amount of a compound of Claim 1.

12. A pharmaceutical composition comprising a
 10 pharmaceutical carrier, and dispersed therein, a therapeutically effective
 amount of a compound of Claim 5.

13. A pharmaceutical composition comprising a
 15 pharmaceutical carrier, and dispersed therein, a therapeutically effective
 amount of a compound of Claim 10.

14. A method for treating prostate cancer which
 comprises administering to a mammal in need thereof a therapeutically
 effective amount of a composition of Claim 11.

15. A method for treating prostate cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 12.

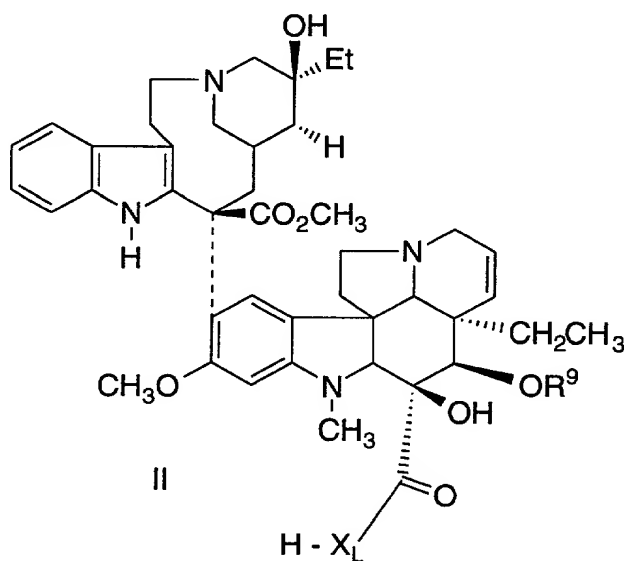
16. A method for treating prostate cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 13.

17. A method for treating benign prostatic hyperplasia which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 11.

18. A pharmaceutical composition made by combining the compound of Claim 1 and a pharmaceutically acceptable carrier.

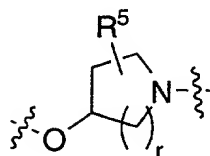
19. A process for making a pharmaceutical composition comprising combining a compound of Claim 1 and a pharmaceutically acceptable carrier.

20. A compound of the formula II:



wherein:

X_L is selected from $-NH-(CR^3_2)_u(CR^4_2)_v-O-$ and



5

R^3 and R^4 are independently selected from: hydrogen, C₁-C₆-alkyl, hydroxylated C₃-C₈-cycloalkyl, polyhydroxylated C₃-C₈-cycloalkyl, hydroxylated aryl, polyhydroxylated aryl and aryl, or

10 one R^3 and one R^4 are combined to form a $-(CH_2)_w-$, which is unsubstituted or substituted with one or two substituents selected from OH and C₁-C₆ alkyl; or

an R^3 is combined with another R^3 on the same carbon to form a $-(CH_2)_x-$; or

15 an R^4 is combined with another R^4 on the same carbon to form a $-(CH_2)_x-$;

R^5 is selected from OH and C₁-C₆ alkyl;

20 R^9 is hydrogen, (C₁-C₃ alkyl)-CO, or chlorosubstituted (C₁-C₃ alkyl)-CO; and

r is 1, 2 or 3;

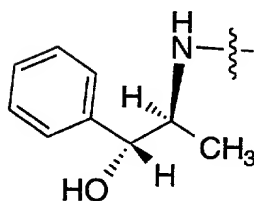
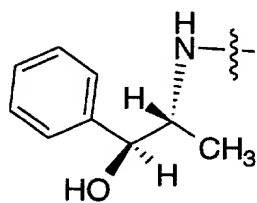
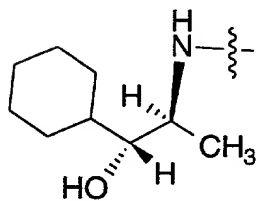
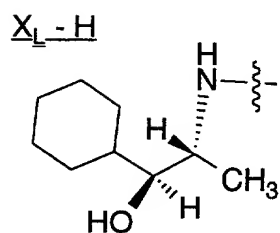
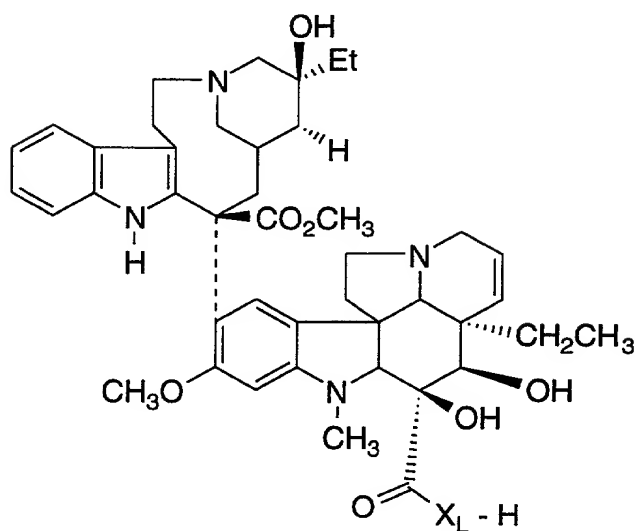
u and v are independently selected from: 0, 1, 2 or 3;

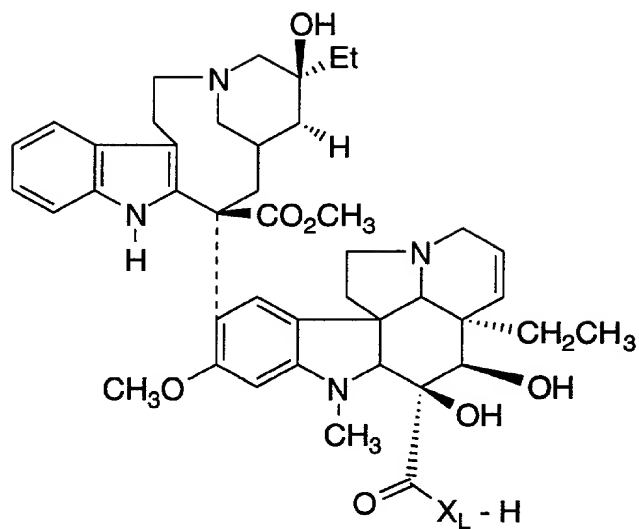
25 w is 2, 3 or 4;

x is 3, 4 or 5;

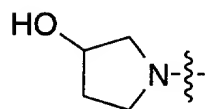
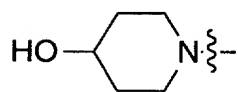
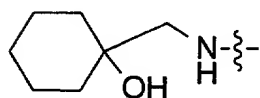
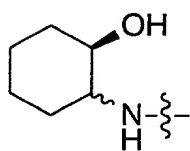
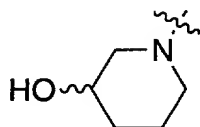
or the pharmaceutically acceptable salt or optical isomer thereof.

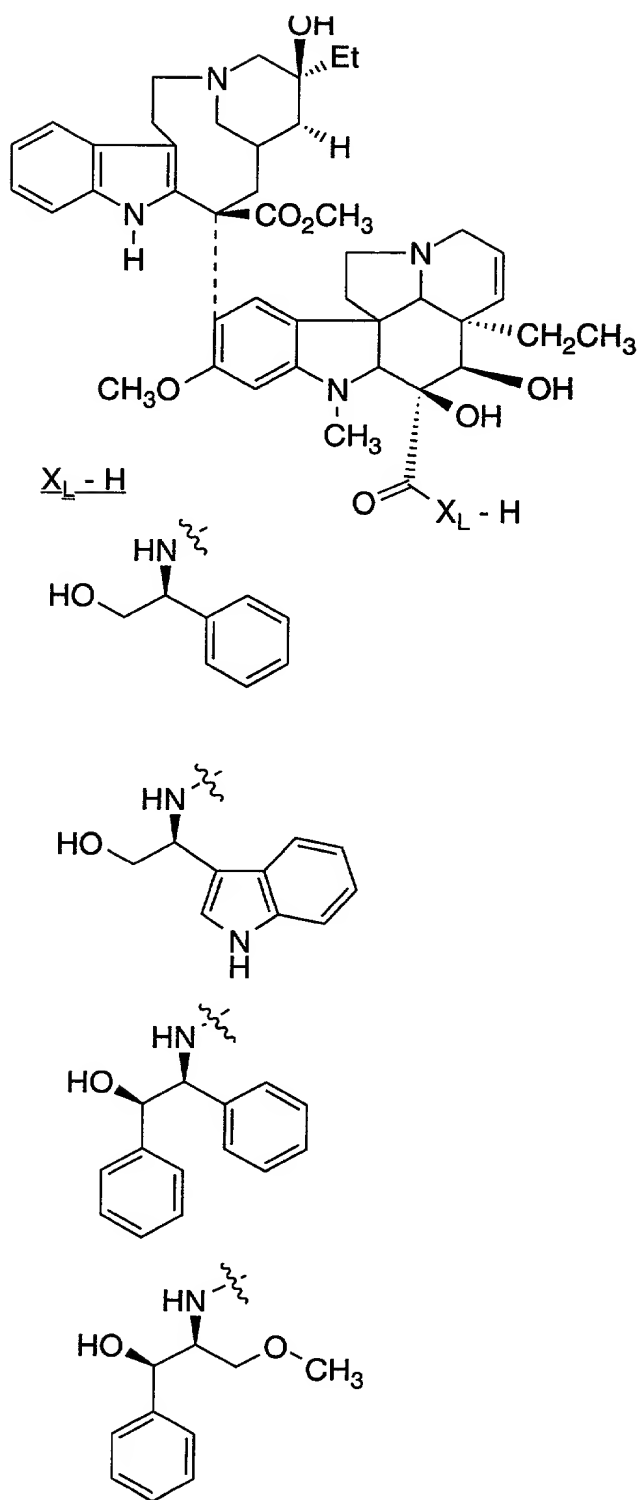
21. The compound according to Claim 20 selected from:





$\text{X}_\text{L}-\text{H}$





or the pharmaceutically acceptable salt thereof.

22. A pharmaceutical composition comprising a
pharmaceutical carrier, and dispersed therein, a therapeutically effective
5 amount of a compound of Claim 20.

23. A pharmaceutical composition comprising a
pharmaceutical carrier, and dispersed therein, a therapeutically effective
10 amount of a compound of Claim 21.

24. A method for treating cancer which comprises
administering to a mammal in need thereof a therapeutically effective
amount of a composition of Claim 22.

25. A method for treating cancer which comprises
15 administering to a mammal in need thereof a therapeutically effective
amount of a composition of Claim 23.

T08080" 42842660